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BY OVERNIGHT COURIER

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

RE: Comments on FDA Guidance for Industry: Botanical Drug Products
Docket No. 00D-1392

Enclosed (in duplicate) are PharmaPrint's comments on the draft Guidance for Industry for Botanical Drug Products, in response to the Federal Register Notice, published August 11, 2000.

Sincerely,

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Enclosures (2 copies)

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COMMENTS ON
FDA GUIDANCE FOR INDUSTRY: BOTANICAL DRUG PRODUCTS
Announced in Federal Register Vol. 65, No. 156, p. 49247, August 11, 2000
Docket No. 00D-139

1.0 GENERAL COMMENTS ON GUIDANCE DOCUMENT

1.1 Supportive of the draft Guidance Document

PharmaPrint, Inc. (hereafter referred to as PharmaPrint) appreciates the efforts placed in drafting this guidance document. PharmaPrint recognizes the need for this document to clearly delineate the steps necessary for the development and approval of botanical drug products. This guidance should also encourage consistency in requirements and recommendations among the various Reviewing Divisions within the Center for Drug Evaluation and Research for the development and approval of botanical drug products.

1.2 Need for additional, more specific guidelines

Very specific guidelines regarding the development of new chemical entities covering the chemistry, manufacturing and controls of drug substances have been previously issued by the FDA. Will such complete detailed guidelines eventually be available for the development of Botanical Drug Products?

1.3 Query: FDA's enforcement policy *vis a vis* dietary supplements

What will be the FDA's enforcement policy, if during the course of development of a botanical, a company provides the agency with information that would indicate a public health safety issue for botanicals currently marketed as functional foods or dietary supplements (under DSHEA)?

The following comments apply to specific issues addressed in the guidance document:

2.0 GENERAL REGULATORY APPROACHES / POLICIES

2.1 Acceptability of OTC Monographs for Certain Botanical Drug Products

page 3, A. Marketing Under OTC Monograph Versus Approved NDA; 1st ¶

"A botanical product that has been marketed in the United States for a material time and to a material extent for a specific OTC drug indication may be eligible for inclusion in an OTC monograph codified in 21 CFR Parts 331-338. The manufacturer would need to submit a petition to amend the monograph to add the botanical substance as a new active ingredient in accordance with 21 CFR 10.30."

Clarification is needed regarding the standards for the evaluation of safety and efficacy when applied to OTC monograph petitions for botanical drug products. Will those applied for the approval of a botanical product New Drug Application be applied to these? This is important since it reflects the fact that, unlike today's traditional pharmaceutical drugs, which first are approved through the IND/NDA process, it is possible that a Botanical Drug could circumvent this important process.

2.2 Acceptability of ANDAs for Botanical Drug Products

page 3, footnote 4

"An applicant may submit an ANDA for a botanical drug product that is the same drug for the same indication as a previously approved drug product. The *generic* version of the previously approved drug

would have to be both pharmaceutically equivalent and bio-equivalent to such drug."

Clarification is needed regarding what standards will be used to determine the pharmaceutical and bioequivalency of a generic version of a botanical drug to one that is the subject of an approved NDA. The guidance does not require pharmacokinetic studies (page 16), if infeasible, for a botanical NDA. In addition, traditional bioequivalency studies probably will not measure all potential active constituents of a botanical drug product. Therefore, what standards will be applied for the demonstration of bioequivalency of a generic version of a botanical drug product previously approved under section 505 of the Act? The acceptance of ANDAs for botanical products appears to be inconsistent with the stipulations delineated in the guidance document. In addition, what criteria will the agency use to determine the pharmaceutical equivalency of a generic version to that of the originally NDA-approved botanical drug?

3.0 CHEMISTRY, MANUFACTRUING AND CONTROLS

3.1 Quality control tests

3.1.1 Botanical Raw Material – Phase 3 Clinical Studies

IX. INDs for Phase 3 Clinical Studies of all Botanical Products
B. Chemistry, Manufacturing, and Controls
1. Expanded clinical studies
a. Botanical raw material

page 25; 1st bullet under subsection a

- **Voucher specimen**

"A voucher specimen of the plant or plant parts should be retained for every batch."

The definition of the term "voucher specimen" needs to be clarified. The following scenario represents a typical practice in cultivating plants, under Good Agricultural Practices:

1. The sponsor purchases seeds from a commercial grower and the contract grower uses these seeds for cultivation of the botanical.

2. The seeds from harvest F_1 are used to cultivate plants for harvest $F_2 \rightarrow F_{4,\ etc.}$ A **voucher specimen** of the plants used to produce the seeds for harvest $F_2 \rightarrow F_{4\ (etc.)}$ is maintained by the sponsor.
3. The sponsor maintains **retain samples** of each batch of harvested plant parts (roots, leaves, bark, etc.) (Botanical Raw Material), which are then extracted to produce the Botanical Drug Substance.

Does the term "voucher specimen", as used in the guideline, actually refer to "retain samples" for every batch of harvested Botanical Raw Material? What would be considered to be a "voucher specimen" for plants cultivated from cuttings? In summary, clarification is needed as to the use of the term "voucher specimen" in the guideline. What if the botanical is not amenable to cultivation according to Good Agricultural Practices?

3.1.2 Botanical Drug Substance – Phase 3 Clinical Studies

IX. INDs for Phase 3 Clinical Studies of all Botanical Products
B. Chemistry, Manufacturing, and Controls
1. Expanded Clinical Studies
b. Botanical drug substance
- The *quality control* tests

page 27

- **Biological assay**

Clarification is needed regarding the blanket requirement for a biological assay for the Botanical Drug Substance (BDS) for Phase 3 clinical studies. This is important since botanicals, and their extracts, are complex materials consisting of many chemical constituents and often the biological activity is best understood through activity measurements in an *in vitro* biological assay. Only infrequently can a biological activity be equally defined by measuring the active chemical constituents. These constituents may interact with themselves, or with other "non-active" constituents, when tested in the presence of the total botanical substance impacting their overall activity in that bioassay. This leads to situations where the overall botanical substance biological activity can only be measured by the biological assay. One example where a biological activity can be correlated to the active

constituents, and therefore controlled by either measuring their amount or through a biological assay, is when the sum of the independently tested active constituents biological activity describes the majority of the total botanical substance activity. These types of determination require knowing how much the active constituent is present in the botanical substance and its IC_{50} or EC_{50} measured as a separate entity in that biological assay. If the chemical composition of a BDS is fully characterized, including identification of the active constituents, (> 90% w/w), controlled from batch to batch, and shown to correlate with the biological activity of the BDS would FDA still require a biological assay for Quality Control (QC) release of the BDS?

Biological assays are inherently variable in nature (10 to 20%, depending on the assay). Thus, clarification is needed as to the range of variability that FDA will accept for biological assays used for QC release of the Botanical Drug Substance. Clarification is also needed in defining what is an acceptable reference standard for the biological assay. A requirement of the use of standards known to be pharmacologically active is often inappropriate since there is usually a dramatic difference in receptor or enzyme affinity when considering the potency of the identified biologically active botanical constituent(s).

3.1.3 Botanical Drug Product – Phase 3 Clinical Studies

IX. INDs for Phase 3 Clinical Studies of all Botanical Products
B. Chemistry, Manufacturing, and Controls
1. Expanded clinical studies
c. Botanical drug product
• The *quality control* tests

▪ **Chemical identification**

page 28 (last bullet) and page 29 (first bullet)

" The quality control tests, including, but not limited to, the following specifications:

- **Chemical identification by spectroscopic or chromatographic fingerprints**

- **Chemical identification for the active constituents or, if unknown, the characteristic markers"**

Clarification is needed regarding the last sentence of page 28 and the first sentence on page 29. Why are two identification tests required for the release of Botanical Drug Products? Typically only one identification test is sufficient to release synthetic drug products. Since the drug substance (extract) will be well characterized only one identity test for the Botanical Drug Product should be sufficient. The identity test should provide an easy method to confirm the identity of the drug product, for example, chemical identification for the active ingredient or characteristic markers. Chemical fingerprints are very complicated and don't provide any additional benefit over the simpler chemical identification using an active ingredient or characteristic marker constituent.

- ***Biological Assay for Botanical Drug Product***

page 29; 3rd bullet

Why is a biological assay needed for the quality control of the Botanical Drug Product (BDP), if it is employed for the QC release of the Botanical Drug Substance (BDS, page 26) used for formulating the BDP? Strength and content uniformity of the BDP should be defined by "Weight" and "Content of Biological/ Characteristic Markers". How would possible interferences arising from excipients, carriers or other compounds used in the final formulation be handled if they impact the overall activity of the BDP compared to the activity of the BDS?

3.1.4 Botanical Drug Products – NDA Considerations

IX. INDs for Phase 3 Clinical Studies of All Botanical Products
B. Chemistry, Manufacturing, and Controls
2. End-of-Phase 3 Clinical Studies and Pre-NDA Considerations

page 30, ¶ c

c. Batch-to-batch consistency

"... All chemical constituents present in the drug substance batches should be qualitatively and quantitatively comparable based on spectroscopic and/or chromatographic fingerprinting."

Botanical constituents are frequently very diverse ranging both in molecular weight and polarity. Such diversity of compounds would require multiple fingerprints, which in turn would require complex comparisons that are not practical as a qualitative measurement.

Quantitative comparison of fingerprints requires sophisticated data management and analysis. Since quantitative comparisons will require specifications, how will these specifications be established for complex fingerprints? Fingerprints usually contain dozens of peaks, which can vary depending on the analytical methodology and the nature of botanical products. Determining pass/fail for this complex system will be challenging and possibly not feasible.

In my opinion, if a fingerprint requirement is necessary it should be made flexible and less rigorous. The entire CMC package (strict quality controls of the Botanical Raw Material, process validation, analytical methods, specifications, in-process controls, etc) should be evaluated for product control and a specific fingerprint requirement should not be defined unless no other avenue is possible for adequate control of that product. This determination should be made on a case-by-case basis.

page 30, ¶ e

e. Mass balance of the test sample

"... Analytical methods used for fingerprinting should be capable of detecting as many chemical constituents as possible. Multiple fingerprints, using a combination of analytical methods with different separation principles and test conditions, may be useful. Additionally, the analytical methods in combination should be able to demonstrate the mass balance of the test sample."

Linking different fingerprints to determine mass balance for an extract would require identification of all constituents, production of reference standards for each constituent and management of extensive data generated by these fingerprints. Since constituent variability is inherent in botanical extracts, employing fingerprints for

mass balance calculations would not prove useful as a control for many of the more complex botanical products. More flexibility in meeting this important requirement might be addressed by allowing classes of compounds to be determined quantitatively and used to establish a mass balance. For example, methods exist to routinely quantitate total fatty acids, total carbohydrates, etc. These methods can quantitate individual constituents from each class of compounds. Use of totals for classes of compounds as the basis for mass balance seems a reasonable method. Additional mass balance components could include individual active constituents, major inactive metabolites and other prevalent compounds. This list would change depending on the nature of the botanical material but the goal would be to establish a mass balance accounting for all significant components. This would serve to chemically characterize the extract and allow for determination of lot-to-lot performance, reflected in the specification ranges for the extract constituents.

3.2 Stability-indicating assay

IX. INDs for Phase 3 Clinical Studies of All Botanical Products
B. Chemistry, Manufacturing, and Controls
2. End-of-Phase 3 Clinical Studies and Pre-NDA Considerations
g. Stability-indicating analytical methods

page 30, ¶ g.

"The stability of a botanical drug substance or product generally should not be based entirely on the assay of the active constituents, assay of the characteristic markers, or biological assay, because degradants formed during storage from other chemical constituents in the botanical drug substance or product should also be controlled."

The degradants resulting from forced degradation of botanical materials are likely to be very complex and difficult to interpret. The composition of many botanical products will include active constituents and/or marker compounds as well as primary metabolites such as carbohydrates, amino acids and fatty acids. Forced degradations studies on this type of botanical mixture will yield complex, chemically diverse degradation products, which will

be difficult to detect with one analytical method. Likewise, a chromatographic fingerprint would require comparison of complex peak patterns and quantitative determination of the amount of degradation at each stability time point. An appropriate stability program for botanical products will be highly dependent on the nature of the botanical product. Flexibility in defining stability requirements is important and such programs should be negotiated with the agency, on a case-by-case basis.

3.3 Manufactured in accordance with drug CGMPs

IX. INDs for Phase 3 Clinical Studies of All Botanical Products
B. Chemistry, Manufacturing, and Controls
2. End-of-Phase 3 Clinical Studies and Pre-NDA Considerations
i. *CGMPs* as set forth in 21 CFR Parts 210 and 211

page 31, ¶ i.

"The manufacturing and testing facilities for the drug substance and drug product should be ready for FDA inspection to determine if they are in conformance with CGMPs as set forth in 21 CFR Parts 210 and 211."

The ICH GMP Guideline states that plant harvesting, plant cutting and initial extraction are not governed by the GMP guideline, implying that GMP is not required for these steps. This appears to be in conflict with the FDA's Botanical Guideline, which requires GMP compliance for manufacturing facilities for the botanical extract. I would like clarification of this point.

3.4 Environmental Impact Analysis

IX. INDs for Phase 3 Clinical Studies of All Botanical Products
B. Chemistry, Manufacturing, and Controls
2. End-of-Phase 3 Clinical Studies and Pre-NDA Considerations
j. EA

page 31, ¶ j.

"The Agency regards the submission of an NDA for a drug derived from plants taken from the wild as an extraordinary circumstance requiring the submission of an EA."

If crude extracts, derived from wild plants, are purchased from commercially available sources and used as the starting material for further processing into a Botanical Drug Substance will an EA still be required? Some plants, already in commerce for dietary supplements exist in their natural habitat on private lands (e.g. Saw Palmetto). These lands are maintained to keep the plants in their natural state for commercial reasons and are not, technically, cultivated. Do these plants fall under the definition of "wild"?

4.0 PRECLINICAL SAFETY ASSESSMENT

IX. INDs for Phase 3 Clinical Studies of All Botanical Products
C. Preclinical Safety Assessment (including Pre-NDA)

page 34, 2nd full ¶

5. Carcinogenicity Studies

"Carcinogenicity studies may be needed to support marketing approval of a botanical drug, depending on the duration of therapy or any specific cause for concern."

In the absence of compelling information indicating an absolute need for a two-year carcinogenicity study, and determination that one is even necessary, can the study begin after approval of the NDA?